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First-in-Human Evaluation of Anti–von Willebrand Factor Therapeutic Aptamer ARC1779 in Healthy Volunteers

James C. Gilbert, MD; Tia DeFeo-Fraulini, MS; Renta M. Hutabarat, PhD; Christopher J. Horvath, DVM; Patricia G. Merlino, MS; H. Nicholas Marsh, PhD; Judith M. Healy, PhD; Sleiman BouFakhreddine, MD; Thomas V. Holohan, MD; Robert G. Schaub, PhD

Background—ARC1779 is a therapeutic aptamer antagonist of the A1 domain of von Willebrand Factor (vWF), the ligand for receptor glycoprotein 1b on platelets. ARC1779 is being developed as a novel antithrombotic agent for use in patients with acute coronary syndromes.

Methods and Results—This was a randomized, double-blind, placebo-controlled study in 47 healthy volunteers of doses of ARC1779 from 0.05 to 1.0 mg/kg. Pharmacodynamic effects were measured by an ELISA for free vWF A1 binding sites and by a platelet function analyzer. In terms of pharmacokinetics, the concentration-time profile of ARC1779 appeared monophasic. The observed concentration and area under the curve were dose proportional. The mean apparent elimination half-life was \(\text{H11015}\) 2 hours, and mean residence time was \(\text{H11015}\) 3 hours. The mean apparent volumes of distribution (at steady state and during terminal phase) were approximately one half the blood volume, suggesting that ARC1779 distribution is in the central compartment. The mean clearance ranged from \(\text{H11015}\) 10% to \(\text{H11015}\) 21% of the glomerular filtration rate, suggesting that renal filtration may not be a major mechanism of clearance of ARC1779. Inhibition of vWF A1 binding activity was achieved with an EC\(_{90}\) value of \(\text{H9262}\) 2.0 g/mL (151 nmol/L) and of platelet function with an EC\(_{90}\) value of \(\text{H9262}\) 2.6 g/mL (196 nmol/L). ARC1779 was generally well tolerated, and no bleeding was observed. Adverse events tended to be minor and not dose related.

Conclusions—This is the first-in-human evaluation of a novel aptamer antagonist of vWF. ARC1779 produced dose- and concentration-dependent inhibition of vWF activity and platelet function with duration of effect suitable for the intended clinical use in acute coronary syndromes. (Circulation. 2007;116:2678-2686.)

Key Words: aptamers, nucleotide ■ pharmacokinetics ■ pharmacology ■ platelets ■ thrombosis ■ von Willebrand factor

von Willebrand factor (vWF)—dependent platelet adhesion and aggregation can occur at sites of vascular injury and endothelial denudation, where exposed and fluid-phase vWF is activated to promote thrombosis by several mechanisms.\(^1\,^2\) Shear stress in conduit arteries can be elevated at sites of stenosis,\(^3\,^4\,^5\) leading to activation of vWF, triggering vWF-platelet binding, and generating procoagulant platelet-derived microparticles.\(^6\,^7\) In the absence of high shear force, eg, in the capillary or venous circulation, vWF is not activated, and its contribution to thrombogenesis is greatly reduced.\(^1\,^2\)

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vWF binds to collagen via its A3 domain and binds to platelets via its A1 or C3 domain to form homotypic multimers between matrix-bound and soluble vWF molecules.\(^8\) Under the conditions of high shear force present in the arterial circulation, vWF is activated by means of a physical deformation that exposes its A1 domain and enables binding to the platelet glycoprotein (GP) Ib receptor.\(^9\) Anti-vWF aptamer ARC1779 binds the A1 domain of activated vWF and inhibits its interaction with the GPIb receptor on platelets, inhibiting all of the vWF-mediated activation pathways and potentially blocking pathological thrombosis.

In addition to its potential as an effective antithrombotic therapeutic principle, vWF antagonism also could offer an improved risk-to-benefit ratio compared with GPIIb/IIIa receptor antagonism for use in the management of acute coronary syndromes (ACS) and in conjunction with percutaneous coronary intervention (PCI) procedures.\(^10\,11\)

Results of first-in-human phase 1 clinical investigation of the safety and tolerability of ARC1779 in healthy subjects are described in this report.

Methods

Study 1779–06–001 was a 2-part, randomized, double-blind, placebo-controlled, dose-escalation study that evaluated 5 single
doses of ARC1779 administered as an intravenous bolus or as a 15-minute "slow intravenous bolus" (part A) and 1 dose of ARC1779 given as a slow intravenous bolus followed by a 4-hour infusion (part B; slow IV bolus plus infusion).

Study Drug
ARC1779 is a synthetically manufactured aptamer conjugated to a polyethylene glycol (PEG; molecular weight, 20 kDa) moiety at the 5′ terminus. The proposed secondary structure of ARC1779 is depicted in Figure 1. ARC1779 binds to the A1 domain of human vWF with high affinity, preventing interaction with platelet GPIb. The core aptamer portion of ARC1779 (molecular weight, ~33 kDa), is a synthetically manufactured, modified DNA/RNA aptamer (26 modified 2′-O-methyl-nucleotides, 26 modified 2′-deoxy nucleotides, 26 modified 2′-O-methoxy nucleotides; ps, phosphorothioate linkage; and i, inverted deoxymimidine).

Study Subjects
Healthy male or female volunteer subjects, 18 to 65 years of age, who met all inclusion/exclusion criteria were enrolled in the study. Female subjects were to be of nonchildbearing potential. The upper limit of body weight permitted for subjects was 110 kg. Among other criteria, subjects were known not to have taken aspirin or aspirin-containing medications within 7 days before the study. The study excluded subjects with any clinically significant medical disorder; tendency to bleed easily; history of recent trauma or surgery; abnormal laboratory parameters for liver, renal, or coagulation function and platelet count; or cutaneous bleeding time (CBT) >15 minutes.

Study Design
The study protocol was approved by the institutional review board, and all subjects provided written informed consent before receiving any treatments. Within dosing cohorts of parts A and B, subjects were randomized (5:1) to either a single intravenous dose of ARC1779 or placebo (sodium chloride injection 0.9%, United States Pharmacopeia). ARC1779 was given to subjects according to weight-adjusted regimens with dosing on study day 0. Subjects were discharged from the clinic after safety evaluations on day 2 and were instructed to return on day 7 for follow-up.

The study design is depicted in Figure 2. Part A assessed the safety, tolerability, pharmacokinetics, and pharmacodynamics relative to placebo of 5 ascending dose levels of ARC1779 (0.05, 0.1, 0.3, 0.6, or 1.0 mg/kg), each administered as a single intravenous bolus. In the original protocol, part A was expected to enroll 30 subjects (5 cohorts with 6 subjects in each cohort). However, after completion of cohorts 1 and 2 (0.05 and 0.1 mg/kg) and dosing of 5 subjects enrolled in cohort 3 (0.3 mg/kg), the method of bolus administration was modified as a result of a hypersensitivity reaction that occurred in 1 subject at a dose of 0.3 mg/kg given by rapid intravenous push at a concentration of 10 mg/mL. Thereafter, ARC1779 was diluted (to a maximal concentration of 3.7 mg/mL) and the rate of administration was reduced so that it was given as a slow intravenous bolus over 15 minutes. Additional subjects were enrolled in new cohorts (cohorts 4 and 5) at the 0.1- and 0.3-mg/kg dose levels to allow evaluation of ARC1779 at these doses by the slow intravenous bolus method. Subsequently, dose escalation to 1.0 mg/kg was completed without another such reaction. As a result of these changes, part A enrolled 41 subjects (7 cohorts with 6 in each cohort, except for cohort 3, which had 5 subjects; see Table 1). To minimize risk to study subjects, safety and tolerability data collected up to and including day 2 were reviewed at each dose level before escalation to the next dose level. Part B evaluated a single dose level of ARC1779 administered according to a slow IV bolus plus infusion regimen and enrolled a single cohort of 6 subjects randomized (5:1) to either ARC1779 or placebo. ARC1779 was given to subjects in part B as an initial slow intravenous bolus of 0.3 mg/kg over 15 minutes.
Table 1. Dosing Cohorts for Part A (n=41) and Part B (n=6) of Study 1779–06–001 (n=47)

<table>
<thead>
<tr>
<th>Part</th>
<th>Cohort</th>
<th>Dose, mg/kg</th>
<th>Administration Method</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1</td>
<td>0.05</td>
<td>IV push</td>
<td>6</td>
</tr>
<tr>
<td>A</td>
<td>2</td>
<td>0.1</td>
<td>IV push</td>
<td>6</td>
</tr>
<tr>
<td>A</td>
<td>3</td>
<td>0.3</td>
<td>IV push</td>
<td>5</td>
</tr>
<tr>
<td>A</td>
<td>4</td>
<td>0.1</td>
<td>Slow IV bolus</td>
<td>6</td>
</tr>
<tr>
<td>A</td>
<td>5</td>
<td>0.3</td>
<td>Slow IV bolus</td>
<td>6</td>
</tr>
<tr>
<td>A</td>
<td>6</td>
<td>0.6</td>
<td>Slow IV bolus</td>
<td>6</td>
</tr>
<tr>
<td>A</td>
<td>7</td>
<td>1.0</td>
<td>Slow IV bolus</td>
<td>6</td>
</tr>
<tr>
<td>B</td>
<td>8</td>
<td>0.6</td>
<td>Slow IV bolus + infusion</td>
<td>6</td>
</tr>
</tbody>
</table>

minutes, followed by infusion of an additional 0.3 mg/kg over 4 hours to provide a total dose of 0.6 mg/kg.

Clinical Assessments
For all subjects, the safety of ARC1779 was assessed through evaluation of adverse events, vital signs, 12-lead ECG recordings, physical examinations, clinical laboratory results, CBT, and complement system activation. Safety parameters were assessed serially during the study through day 2 and at the follow-up visit on day 7. Physical examinations, performed frequently during the study and before discharge on day 2, included assessment of external bruising or mucosal bleeding. CBT was measured as a proxy for bleeding risk potentially associated with ARC1779 and was determined by the standard template method (with a maximal period of observation of 20 minutes). Plasma concentrations of complement protein fragment C3a were quantified to assess complement system activation. C3a analyses were performed by IBT Laboratories (Lenexa, Kan).

Measurement of vWF Activity
The inhibitory effect of ARC1779 on vWF activity (a measure of the amount of active ["free"] vWF with functional A1 domain present in plasma) was evaluated serially during the study with a commercially available quantitative direct ELISA kit (READDS vWF Activity ELISA Test Kit, Corgenix, Inc, Westminster, Colo), with results reported as a percentage of vWF activity. The relative vWF activity was expressed (normalized) as a percentage of baseline values (100%). The relative (percentage) inhibition of normalized vWF activity also was calculated as follows: 100% - % activity = % inhibition.

Measurement of Platelet Function
The effect of ARC1779 on vWF-mediated, shear-dependent platelet function was evaluated with the Platelet Function Analyzer (PFA-100) instrument (Dade Behring, Inc, Deerfield, Ill) and samples of whole venous blood anticoagulated with 3.2% sodium citrate. Each blood sample was placed in a test cartridge and aspirated through a capillary (200-μm diameter) under constant negative pressure (high shear stress) toward a membrane with a small aperture (150-μm diameter) coated with equine type I collagen to activate platelets and adenosine 5'-diphosphate (C/ADP cartridges) to enhance platelet aggregation. The reported value, PFA-100 closure time, represents the elapsed time in seconds (up to a maximum of 300 seconds) until aperture occlusion by formation of a platelet plug.

Measurement of ARC1779 Plasma Concentration
Plasma concentrations of ARC1779 were determined serially during the study with a validated high-performance liquid chromatography assay with ultraviolet detection. The lower limit of quantification of the high-performance liquid chromatography/ultraviolet assay was 0.25 μg/mL, with a linear range from 0.25 to 200 μg/mL.

Analysis of Concentration-Time Data
Noncompartmental analysis of ARC1779 concentration-time profiles was performed with WinNonlin, version 5.1 (Pharsight Corp, Mountain View, Calif) to derive estimates of pharmacokinetics parameters. The pharmacokinetics parameters evaluated in the study included the maximum observed concentration (Cmax), the time to maximum observed concentration (Tmax), elimination half-life (t1/2), area under the curve (AUC) to the last quantifiable time point (AUC0–tn), AUC extrapolated to infinity (AUC0–∞), and volume of distribution during terminal phase (Vt).

Pharmacokinetics/Pharmacodynamics Correlation
ARC1779 plasma concentrations and normalized values for percent inhibition of vWF activity or platelet function were fitted to an Emax model with the following equation: E=Eo+(Emax−Eo)·[C/C+EC50].

Statistical Considerations
The number of subjects enrolled in the study was typical of a phase I dose-escalation design. No formal statistical analysis or hypothesis testing was performed.
All subjects completing pharmacokinetics serial sampling for a given dose were included in the pharmacokinetics analysis set. All randomized subjects who received an intravenous injection were included in the safety analysis set. Pharmacokinetics and safety analyses included subject characteristics variables, pharmacokinetic and pharmacodynamic variables, pharmacokinetic/pharmacodynamic modeling, and safety variables. For part A, descriptive statistics (number, mean, SD, median, minimum, maximum), frequencies, and percentages were calculated by treatment group. Data analyses were performed with SAS version 8.2 (SAS Institute Inc, Cary, NC).

The authors had full access to and take responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results
Subject Disposition, Demographics, and Baseline Characteristics
A total of 47 healthy subjects were enrolled in the study and were dosed with ARC1779 or placebo. Of this total, 41 subjects participated in the dose-escalation arm (part A) and 6 subjects participated in the bolus plus infusion arm (part B), according to the dosing regimen outlined in Table 1. Overall, the placebo and active treatment (ARC1779) groups were similar in terms of demographic and baseline characteristics. In both parts A and B, men represented the majority (97% and 100%, respectively) of subjects in the active treatment groups. Additional demographic and baseline characteristics of subjects in parts A and B are summarized in Table 2.

Safety
ARC1779 was generally well tolerated. There were no deaths, serious adverse events, or premature withdrawals from treatment as a result of adverse events. Adverse events were infrequent and mild in severity, with the exception of 1 subject at 0.3 mg/kg who had a hypersensitivity reaction of moderate severity to the intravenous push administration of undiluted ARC1779 solution for injection. This hypersensitivity reaction was associated with typical gastrointestinal and cardiovascular manifestations, with marked activation of the complement system. The reaction resolved rapidly without treatment and without sequelae. Subsequently, the method of
administration of ARC1779 was modified by both ≥3-fold dilution of the concentration of the injected drug solution and slowing of the rate of delivery from intravenous push to a 15-minute slow intravenous bolus. After these modifications, no additional cases of hypersensitivity reactions occurred, despite ≥3-fold dose escalation. There were no clinically significant findings related to ARC1779 in a battery of routine safety surveillance parameters, including vital signs, ECGs, urinalysis, and hematologic and chemistry laboratory tests. ARC1779 was not associated with prolongation of activated partial thromboplastin time, a possible oligonucleotide-related class effect.

Pharmacokinetics Profile
Mean plasma concentrations of ARC1779 over time for the intravenous push and slow intravenous bolus groups are shown in Figure 3A and 3B. The concentration-time profiles of ARC1779 appeared monophasic, although the elimination phase may not have been fully captured because of the sensitivity of the high-performance liquid chromatography/ultraviolet bioanalytical method. The mean apparent pharmacokinetics parameters, estimated by noncompartmental analysis of concentration-time profiles, showed that there were linear and dose-proportional increases in mean C$_{\text{max}}$, AUC$_{0-\text{last}}$, and AUC$_{0-\infty}$. Maximal exposure to ARC1779 was produced by 1.0-mg/kg slow intravenous bolus administration, which gave a mean C$_{\text{max}}$ of 21.2 μg/mL and a mean AUC$_{0-\infty}$ of 80.9 μg · h$^{-1}$ · mL$^{-1}$. T$_{\text{max}}$ was ≈7 to 10 minutes after the intravenous push and ≈30 minutes after the slow intravenous bolus administration. The elimination half-life of ARC1779 (t$_{1/2}$) was ≈2 hours, the mean residence time was ≈3 hours, and volumes of distribution (V$_{\text{d}}$ and V$_{\text{ss}}$) across the dose range examined were approximately one half of the blood volume in humans (≈74.3 mL/kg$^{12}$), suggesting that ARC1779 was
Inhibition of vWF Activity

The inhibitory effect of ARC1779 on plasma vWF activity was characterized in terms of the amount of active ("free") vWF with functional A1 domain present in plasma (see Methods).

Plots of the mean percentage of vWF activity over time for the intravenous push, slow intravenous bolus, and slow intravenous bolus plus infusion groups are shown in Figure 4A, 4B, and 4C, respectively. vWF activity was inhibited in a dose-dependent manner after single-dose intravenous push or slow intravenous bolus administration with rapid onset of action and gradual restoration of vWF activity by 12 to 24 hours after dose. After a 15-minute slow intravenous bolus, the extent of inhibition of vWF activity for all of the doses reached a maximum by 1 to 2 hours and ranged from ≈60% for the 0.1-mg/kg dose to >95% for the 1.0-mg/kg dose. Inhibition of vWF activity to ≈3% of baseline, or the lower limit of quantification of the assay, was achieved and sustained for at least 4 hours with 1.0 mg/kg ARC1779. Inhibition of vWF activity to ≈5% of baseline was achieved and maintained for nearly this same duration with 0.6 mg/kg ARC1779. The regimen of a slow intravenous bolus plus 4-hour infusion maintained maximal vWF inhibition throughout the 4-hour infusion period, with return to <90% inhibition by ≈8 hours after dose and return to baseline by 12 to 16 hours after dose.

Inhibition of Platelet Function

The effect of ARC1779 on vWF-mediated, shear-dependent platelet function was evaluated with the PFA-100 instrument (see Methods). Plots of mean PFA-100 closure time for the intravenous push, slow intravenous bolus, and slow intravenous bolus plus infusion groups are shown as a function of time in Figure 5A, 5B, and 5C, respectively. Platelet function was evaluated with the PFA-100 instrument, the effect of ARC1779 on vWF activity and maintained for nearly this same duration with 0.6 mg/kg ARC1779. The regimen of a slow intravenous bolus plus 4-hour infusion maintained maximal vWF inhibition throughout the 4-hour infusion period, with return to <90% inhibition by ≈8 hours after dose and return to baseline by 12 to 16 hours after dose.

Table 3. Mean Pharmacokinetic Parameter Estimates for ARC1779 in Healthy Volunteers

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameters</th>
<th>IV Push, Total Dose, mg/kg</th>
<th>15-Minute Slow IV Bolus, Total Dose, mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.05</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>0.2 ± 0.5</td>
<td>0.2 ± 0.2</td>
</tr>
<tr>
<td>t(1/2) h</td>
<td>2.5 ± 0.7</td>
<td>2.2 ± 0.4</td>
</tr>
<tr>
<td>T(max) h</td>
<td>0.1 ± 0.1</td>
<td>0.1 ± 0.1</td>
</tr>
<tr>
<td>C(max) µg/mL</td>
<td>9.2 ± 1.1</td>
<td>14.6 ± 1.9</td>
</tr>
<tr>
<td>AUC(0-\infty) µg h · h(-1) · mL(-1)</td>
<td>21.7 ± 7.2</td>
<td>46.4 ± 7.9</td>
</tr>
<tr>
<td>C(L) mL · h(-1) · kg(-1)</td>
<td>14.8 ± 5.1</td>
<td>13.4 ± 2.6</td>
</tr>
<tr>
<td>V(ss) mL/kg</td>
<td>31.9 ± 8.1</td>
<td>37.6 ± 4.5</td>
</tr>
</tbody>
</table>

*Mean ± SD pharmacokinetic parameter estimates are reported.
bolus plus infusion administration of ARC1779 was associated with maximal prolongation of PFA-100 closure time that was sustained throughout the 4-hour infusion period, with return to ≥90% inhibition by 8 hours after dose and return to baseline by 16 hours after dose.

Pharmacokinetics/Pharmacodynamics Relationship
The relationship of ARC1779 plasma concentration to inhibition of vWF activity was analyzed by Emax modeling, as shown in Figure 6A and 6B. The fitted EC50 and EC90 values for inhibition of vWF activity after slow intravenous bolus administration of ARC1779 were 0.2 µg/mL (17 nmol/L) and 2.0 µg/mL (151 nmol/L), respectively. The fitted EC50 and EC90 values by Emax modeling for inhibition of platelet function (as measured by prolongation of PFA-100 closure time) after slow intravenous bolus administration of ARC1779 were 0.75 µg/mL (57 nmol/L) and 2.6 µg/mL (196 nmol/L), respectively. These EC50 and EC90 values were in good agreement with those derived from modeling of vWF activity data. However, compared with the vWF activity ELISA, PFA-100 measurements are intrinsically less well suited to recording the maximal pharmacodynamic effects of ARC1779 as a result of a combination of factors: the technical limit of this assay (ceiling, 300 seconds) and its sensitivity to the effect of vWF inhibition (Figure 6B).

Bleeding Risk
There were no bleeding events in the study and no evidence of occult blood loss. As a proxy for bleeding risk, template CBT was measured at baseline and serially during the postdose period. Plots of mean CBT for the intravenous push (A) or slow intravenous bolus administration (B) or part B after slow IV bolus plus infusion administration (C).
In summary, ARC1779 was associated with dose- and concentration-dependent inhibition of plasma vWF activity and platelet function in healthy volunteers after single intravenous bolus administration via intravenous push or slow intravenous bolus with EC90 values of 2 to 3 μg/mL. These plasma ARC1779 concentrations were achieved with single intravenous doses ≥0.1 mg/kg and were sustained for at least 4 hours at single intravenous doses ≥0.3 mg/kg administered as a 15-minute slow bolus. A single intravenous bolus at 0.3 mg/kg followed by 4-hour infusion of an additional 0.3 mg/kg resulted in a mean plasma ARC1779 concentration of ≈4.7 μg/mL during infusion (range, 3.4 to 6.8 μg/mL) and sustained inhibition of vWF activity and platelet function for at least 8 hours.

Discussion

vWF has a prominent role in thrombogenesis in the arterial circulation and is therefore an appealing potential target for pharmacotherapy of ACS and as an adjunct to PCI procedures. vWF not only is a well-established biomarker for the presence of atherosclerotic cardiovascular disease and a prognostic indicator of outcome during and after an acute event but also is now becoming recognized as a mediator of those events because of its causal role in shear-dependent thrombogenesis. Targeting vWF for inhibition is a unique opportunity to improve the therapeutic armamentarium for use in management of ACS and PCI for several reasons. First, the vWF-platelet interaction pathway is independent of other pathways leading to platelet-rich thrombus formation such as platelet activation via the P2Y12 receptor; therefore, the effect of vWF antagonism should be additive to the effects of P2Y12 antagonists such as clopidogrel. Second, because vWF is active only in the presence of the intravascular shear forces found in the arterial-side circulation, a vWF antagonist should act with spatial specificity when antithrombotic efficacy is most needed in ACS, not systemically, thereby potentially avoiding some of the most common hemorrhagic consequences of conventional antiplatelet agents (eg, mucocutaneous bleeding). Finally, a vWF antagonist should modulate the cascade of reactions that culminates in thrombus growth at several of its component steps in a concerted manner, unlike existing antiplatelet agents that are mechanistically tied to 1 step in that cascade. A vWF antagonist should block the activity of both vWF immobilized on subendothelial matrix (the initial step in this sequence) and soluble vWF released into the circulation by shear-activated endothelium and agonist-activated platelets (an intermediate step in this sequence). In addition, through prevention of vWF binding to GPIb, vWF antagonism should block inside-out signaling and upregulation of GPIb/IIIa, thereby preempting the final step in this sequence. Targeting consecutive steps in the cascade of thrombus formation in a concerted manner should
make possible a finer degree of control with less potential for overshoot of inhibition than targeting solely the final step as GPIIb/IIIa antagonists do and should, at the same time, provide more effective control than is possible with inhibition of platelet activation alone.

Aptamers are a novel therapeutic class of oligonucleotides with drug-like properties that share some of the attributes of monoclonal antibodies (resulting in the class being referred to as chemical antibodies), as well as some of those of low-molecular-weight, chemically synthesized drugs.20 ARC1779 is an aptamer antagonist that binds to the A1 domain of vWF with high affinity and blocks vWF-dependent platelet function. Preclinical studies have shown ARC1779 to have limited off-target toxicity and a wide safety margin relative to the exposures needed for antithrombotic efficacy. Furthermore, in a primate model of arterial thrombosis, ARC1779 had antithrombotic efficacy comparable to that of the GPIIb/IIIa antagonist abciximab but did not prolong CBT to the same degree.21 A further potential advantage of ARC1779 relative to GPIIb/IIIa antagonists is the simplicity of administration as a single bolus, without need for sustained post-bolus infusion.

This report describes the pharmacokinetics, pharmacodynamics, safety, and tolerability of ARC1779 in a randomized, placebo-controlled phase 1 study conducted in healthy volunteers. A total of 47 healthy volunteers were treated with a broad range of doses of ARC1779 or placebo in 3 different modes of administration: intravenous push, 15-minute slow intravenous bolus, and 15-minute slow intravenous bolus followed by a 4-hour infusion.

The pharmacokinetics profile of ARC1779 showed a low degree of interindividual variability, simple dose proportionality of exposure, distribution into the plasma component of the central compartment, an apparent half-life of elimination on the order of 2 to 3 hours, and a predominantly nonrenal route of clearance. Gender balance was not achieved in this study; with nearly all volunteers being male; therefore, a confounding effect of gender on the pharmacokinetics analysis cannot be excluded. However, no effect of gender on pharmacokinetics parameters has been observed for ARC1779 in animal studies, and it is unlikely that this limitation alters the fundamental conclusions from the study concerning the pharmacokinetics profile of ARC1779.

The corresponding pharmacodynamic profile of ARC1779 showed extinction of vWF activity as measured by an ELISA designed to detect the availability of vWF A1 domain binding to the platelet GP1b receptor and complete inhibition of shear-dependent, collagen- and ADP-stimulated thrombus formation as measured by a platelet function analyzer device, the PFA-100, with an EC90 for both parameters of 2 to 3 μg/mL. These plasma concentrations of ARC1779 were achieved at Cmax with doses as low as 0.1 mg/kg and were sustained after slow intravenous bolus administration of 1.0 mg/kg for at least 6 hours (Figure 8). The relationship of ARC1779 concentration to inhibition of vWF activity and platelet function was consistent across all doses and dosing regimens.

There were no deaths, serious adverse events, or premature discontinuations due to adverse events in the study. Neither spontaneous bleeding nor bleeding from sites of vascular access was observed. ARC1779 was generally well tolerated, and adverse events were infrequent and mild in all but 1 case, a subject given an intravenous push administration of 0.3 mg/kg at an injected concentration of 10 mg/mL. This subject had a hypersensitivity reaction of moderate severity with activation of the complement system, a phenomenon commonly associated with administration of oligonucleotides in humans.22 This reaction resolved rapidly without intervention and without sequela, but on the basis of this observation and the presumed causal mechanism, ie, drug-induced activation of the alternative pathway of the complement system, the mode of administration of ARC1779 was modified from intravenous push to a slow intravenous bolus infusion given over 15 minutes and at a lower drug concentration. After this slow intravenous bolus mode of administration was introduced, 5 additional cohorts were successfully treated and stepwise dose escalation to 1.0 mg/kg was achieved without a recurrence of any similar reactions.

Conclusions

ARC1779 is a promising new parenteral antithrombotic that represents both a novel therapeutic class (aptamers) and a novel therapeutic mechanism (vWF antagonism). The former...
is expected to confer high specificity for target and low off-target adverse effects; the latter is expected to confer a unique spatial selectivity for the arterial circulation on the basis of shear-dependent regulation of vWF function. This first-in-human clinical trial provides proof of mechanism in terms of inhibition of vWF and platelet function, demonstrates a pharmacokinetics profile well suited for use in the setting of PCI for ACS, and establishes a favorable safety profile for ARC1779. Planned phase 2 investigation of ARC1779 will define the optimal dosing strategy for safety and antithrombotic efficacy in ACS patients undergoing PCI and provide a preliminary, comparative assessment of the therapeutic benefits of vWF or GPIIb/IIIa antagonism.

**Disclosures**

Drs Gilbert, Hutabarat, Marsh, Healy, and Schaub and T. DeFeo-Fraulini, C.J. Horvath, and P.G. Merlino are employees and stockholders of Archemix Corp. The other authors report no conflicts.

**References**


**CLINICAL PERSPECTIVE**

von Willebrand factor (vWF) has a prominent role in arterial thrombogenesis, and the vWF–platelet interaction pathway is independent of other pathways leading to platelet-rich thrombus formation, so targeting vWF for inhibition is a unique therapeutic opportunity. Because vWF is active only in the presence of the shear forces found in the arterial-side circulation, a vWF antagonist should act with spatial specificity, avoiding some of the most common hemorrhagic consequences of conventional antiplatelet therapies. A vWF antagonist should modulate the entire cascade of reactions that culminate in thrombus growth, conferring a finer degree of control with less potential for overshoot of inhibition than with glycoprotein IIb/IIIa antagonists and more effective control than with inhibition of platelet activation alone. Aptamers are a novel therapeutic class of oligonucleotides with drug-like properties. ARC1779 is an aptamer antagonist that binds to the A1 domain of vWF with high affinity and blocks vWF-dependent platelet function. This report describes the pharmacokinetics, pharmacodynamics, safety, and tolerability of ARC1779 in a randomized, placebo-controlled phase 1 study conducted in healthy volunteers. This first-in-human clinical trial provides proof of mechanism in terms of inhibition of vWF and platelet function and demonstrates a pharmacokinetic profile well suited for use in the setting of percutaneous coronary intervention for acute coronary syndromes. There were no deaths, serious adverse events, or premature discontinuations as a result of adverse events in the study. Neither spontaneous bleeding nor bleeding from sites of vascular access was observed. ARC1779 is a promising new parenteral antithrombotic that represents both a novel therapeutic class (aptamers) and a novel therapeutic mechanism (vWF antagonism).